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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/546,201	POLO ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-31 and 33-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-31 and 33-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In paper no. 18, applicant amended claim 26. Claims 26, 28-31 and 33-44 are under consideration.

Request for Continued Examination

The request filed on May 1, 2003 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/546,201 is acceptable and a RCE has been established. An action on the RCE follows.

Drawings

The drawings are objected to because the sequence depicted in Figure 6 is hard to read. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The specification is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific nucleic acid sequences comprising ten or more nucleotides in the specification. Specific examples within the specification that do not comply with the sequence rules are found on pages 25-28. Applicant is required to append a SEQ ID NO. to all sequences applicable to the rule. See 37 CFR § 1.821 (a)-(d) and MPEP § 2422.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28-31 and 33-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 26 has been amended to recite a DNA-dependent RNA polymerase II promoter. Applicant states on page 2 of the response that support for the amendment is found throughout the specification. However, the examiner is unable to find support for the newly added claim limitation in the specification. Therefore, the new limitation presents new matter into the claims. Applicant is required to point to support for the RNA polymerase II promoters that are DNA-dependent or cancel the new matter in response to this rejection. This rejection also affects claims 28-31 and 33-44.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26, 28-31 and 33-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubensky, Jr. et al. (US 6,015,686), which is hereinafter referred to as "Dubensky", Cella et al. (Journal of Experimental Medicine. March 1, 1999; 189 (5): 821-829) and Chada et al. (US 5,736,388).

Claim 26 is drawn to an expression cassette comprising:

1) a promoter operably linked to a nucleic acid molecule, which when transcribed *in vivo*, forms double stranded RNA that induces the production of interferon and

2) a DNA-dependent RNA polymerase II operably linked to a nucleic acid encoding an antigen from a pathogenic agent.

Claims 28 and 29 state that the antigen is a viral antigen selected from HIV, HSV, HBV, HCV, HPV and FIV. Claim 30 states that the pathogenic agent is a bacteria, a parasite or a fungus and claim 31 states that the pathogenic agent is a tumor. Claim 33 requires that the pol II promoter is selected from CMV, SV40, MoMLV LTR and RSV LTR. Claim 34 is drawn to a gene delivery vector comprising the instant expression cassette. Claim 44 is drawn to a cell containing the gene delivery vector of claim 34. Claims 35-43 state that the vector is a plasmid, a recombinant retrovirus, a recombinant herpesvirus, a recombinant poxvirus, a recombinant

adenovirus, a recombinant parvovirus, a recombinant alphavirus, a recombinant polyomavirus, and a eukaryotic layered vector initiation system, respectively.

Dubensky teaches a eukaryotic layered vector initiation system comprising a promoter that expresses a heterologous sequence, see claims 1 and 2. The heterologous sequence is derived from a virus and is selected from HIV, HBV, HCV, FIV, see claim 9, as well as HSV and HPV, see column 4, lines 36-39. Dubensky also teaches that the vector construct can encode proteins from bacteria, parasites or fungus, see column 23, lines 30-36. Additionally, the vector of Dubensky encodes a cancer gene, see column 27, line 60 to column 28, line 2.

The promoter that initiates the synthesis of viral RNA encoding the heterologous gene of Dubensky is selected from the group consisting of the following: CMV, SV40, MoMLV LTR and RSV LTR, see claim 7, column 12, lines 54-62, column 55, lines 14-34, column 100, lines 55-56, column 101, lines 42-57. Although Dubensky does not identify these promoters specifically as DNA-dependent RNA polymerase promoters, these promoters are identical to the promoters listed in instant claim 33, which are described as DNA-dependent RNA polymerase promoters in instant claim 26. Therefore, the promoters encoding the heterologous gene of Dubensky are DNA-dependent RNA polymerase II promoters.

Dubensky teaches that a wide variety of vectors may be utilized in the eukaryotic layered vector initiation system, such as retroviruses, herpesviruses, poxviruses, adenoviruses, parvoviruses, alphaviruses and polyoma viruses, see column 32, lines 26-67. Dubensky also teaches that the expression vector is a plasmid, see column 36, line 44 to column 37, line 16 and column 56, line 47 to column 57, line 11 for example. Dubensky teaches a cell containing the gene delivery vector in claim 12.

Dubensky also teaches that antisense RNA forming large quantities of double-stranded RNA is utilized in the expression system. The double-stranded RNA increases the expression of gamma interferon and boosts the expression of MHC I antigens, see column 23, lines 1-13. Dubensky also claims a vector construct expressing an antisense sequence or a non-coding sequence, see claim 10. The antisense sequence and the non-coding sequence recited in the claim encompass an antisense RNA that forms double-stranded RNA.

Therefore, Dubensky teaches a construct encoding a DNA-dependent RNA polymerase II promoter encoding an antigen from a pathogenic agent, as well as a construct encoding a nucleic acid that forms double-stranded RNA for the induction of interferon, see the previous citations.

Dubensky does not teach a single construct comprising a DNA-dependent RNA polymerase II promoter expressing a heterologous antigen and another promoter encoding a nucleic acid that forms double-stranded RNA.

However, one of ordinary skill in the art at the time the invention was made would have been motivated to express a nucleic acid molecule that forms a double-stranded RNA and a viral antigen in the same construct to stimulate a specific immune response to the viral antigen, see column 37, line 35 to column 38, line 16, and to stimulate the production of interferon, see column 23, lines 5-8 of Dubensky. Cella et al. teach that double-stranded RNA induces interferon, protects against cytopathic effects of a virus in dendritic cells and increases the capacity of dendritic cells to prime T cells, see the abstract and the first two paragraphs in the discussion section on page 826. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to induce the production of interferon with double-stranded RNA to protect dendritic cells from viral infection and generate a CTL response

to a viral infection, see page 821 and the first two paragraphs in the discussion section on page 826 of Cella et al. and elicit a specific immune response with the viral antigen of Dubensky.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a construct comprising a DNA-dependent RNA polymerase II promoter expressing a heterologous antigen and another promoter expressing a double-stranded RNA because Dubensky teaches that the expression vector is used to express multiple heterologous genes, see column 16, line 61 to column 17, line 29 and column 85, line 50 to column 94, line 18. Therefore, the instant construct would have been prima facie obvious in view of the teachings of Dubensky, absent unexpected results to the contrary.

One of ordinary skill in the art at the time the invention was made would also have been motivated to express the heterologous genes of Dubensky from different promoters within the same construct because Chada et al. teach that one promoter within the same construct may be inadequate to ensure an adequate level of expression of all heterologous genes, see column 26, lines 4-21.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in expressing different heterologous genes from different promoters in the same construct of Dubensky because the vector of Chada et al. is also a eukaryotic layered vector initiation system, see column 14, lines 52-56. The eukaryotic layered vector initiation system of Chada et al. utilizes the same viral vectors and the same promoters of Dubensky, see column 16, line 48 to column 17, line 21 of Chada et al. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Response to Arguments

Applicant summarizes the conclusions in the final rejection of July 2, 2002. In the rejection, it was asserted that Dubensky taught all of the elements of instant claim 26, except for expressing a double stranded (ds) RNA in the vector system to induce the production of interferon.

However, upon further consideration of the reference, it is evident that Dubensky teaches that double-stranded RNA increases the expression of gamma interferon and boosts the expression of MHC I antigens, see column 23, lines 1-13. Dubensky also claims a vector construct expressing an antisense sequence or a non-coding sequence, see claim 10. The antisense sequence and the non-coding sequence recited in the claim encompass an antisense RNA that forms double-stranded RNA. Therefore, it is determined that Dubensky teaches all of the recited elements of claim 26. The difference between the instant claims and the teachings of Dubensky is a single construct comprising a promoter expressing a nucleic acid that forms ds RNA and a DNA-dependent RNA polymerase II promoter expressing an antigen from a pathogenic agent. Dubensky teaches different constructs expressing each element separately, see claims 1, 2, 9 and 10 for example.

However, Dubensky and Cella et al. teach motivation to combine the heterologous sequences into one construct. Dubensky teaches that expression of heterologous antigens stimulate a specific immune response to the antigen, see column 37, line 35 to column 38, line 16 and double stranded RNA stimulates the production of interferon, see column 23, lines 5-8 of Dubensky. Cella et al. teach that induction of interferon by double-stranded RNA protects against cytopathic effects of a virus and increases the capacity of dendritic cells to prime T cells,

see the abstract and the first two paragraphs in the discussion section on page 826. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to induce the production of interferon with double-stranded RNA to protect dendritic cells from viral infection and generate a CTL response to a viral infection, see page 821 and the first two paragraphs in the discussion section on page 826 of Cella et al. and elicit a specific immune response with the viral antigen of Dubensky.

The combination of Dubensky and Chada et al. provide further motivation to express the heterologous sequences of Dubensky within the same construct from different promoters to ensure adequante levels of expression of all heterologous genes, see column 26, lines 4-21 of Chada et al.

Therefore, more than one motivation for combining the expression of the heterologous sequences of Dubensky from different promoters within the same construct is specifically taught in the prior art.

A reasonable expectation of success in producing the claimed expression cassette is also found within the prior art. The eukayotic layered vector initiation expression cassette of Dubensky is used to simultaneously express multiple heterologous genes, see column 16, line 61 to column 17, line 29 and column 85, line 50 to column 94, line 18. In addition, Chada et al. teach using different promoters to express different genes within the same multivalent construct to ensure adequate levels of expression of all genes, see column 26, lines 4-21. The teachings of Chada et al. are directly applicable to the construct of Dubensky because both references teach a eukayotic layered vector initiation expression cassette, see claim 1 of Dubensky and column 14, lines 52-56 of Chada et al.

The prior art teaches all of the limitations instantly recited and provides more than one motivation for combining the expression of heterologous genes into a single expression cassette with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Applicant states that the Office action asserts that the motivation to combine the references is found in the teachings of Cella or Polo. However, upon further consideration, it is determined that the teachings of Polo are not relevant in view of the teachings of Dubensky, Cella et al. and Chada et al. Therefore, arguments presented against Polo are not relevant to the instant rejection.

Applicant also discusses the previous assertion in the Office action regarding the classification of the promoters instantly recited.

In response, the conclusion in the Office action regarding the instant promoters is no longer relevant since it is determined that the promoters taught by Dubensky and the instant, recited promoters are the same. That is, the promoters of Dubensky, taught in claim 7, column 12, lines 54-62, column 55, lines 14-34, column 100, lines 55-56, column 101, lines 42-57 are identical to the promoters listed in instant claim 33, which are described as DNA-dependent RNA polymerase promoters in instant claim 26. Therefore, the promoters encoding the heterologous gene of Dubensky are DNA-dependent RNA polymerase II promoters.

Applicant argues that the previous combination of references is completely silent for providing motivation to arrive at an expression cassette comprising two promoters expressing different heterologous sequences. Applicant also argues that the references cited in the previous

rejection do not teach an expression construct comprising two promoters, where the promoter operably linked to the nucleic acid encoding an antigen is an RNA polymerase II promoter.

Applicant's arguments have been considered, but are found unpersuasive because the prior art provides more than one motivation for arriving at an expression cassette comprising two promoters expressing different heterologous sequences. One of ordinary skill in the art at the time the invention was made would have been motivated to induce the production of interferon with double-stranded RNA to protect dendritic cells from viral infection and generate a CTL response to a viral infection, see page 821 and the first two paragraphs in the discussion section on page 826 of Cella et al. and elicit a specific immune response with the viral antigen of Dubensky. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to express heterologous sequences of Dubensky within the same construct from different promoters to ensure adequate levels of expression of all heterologous genes, see column 26, lines 4-21 of Chada et al.

With respect to the RNA polymerase II promoters, the CMV, SV40, MoMLV LTR and RSV LTR promoters of Dubensky in claim 7, column 12, lines 54-62, column 55, lines 14-34, column 100, lines 55-56, column 101, lines 42-57 are identical to the instant promoters recited. Therefore, Dubensky teaches that the promoter operably linked to the nucleic acid encoding an antigen in claim 1 is an RNA polymerase II promoter.

Applicant also asserts that the Office cannot rely on a high level of skill in the art to supply motivation to combine selected elements in the references. Applicant cites case law to support this assertion.

Applicant's arguments have been considered. The Office agrees with the conclusions of the case law cited by applicant. The instant rejection does not rely on a high level of skill, but motivation explicitly taught in the prior art references of Dubensky, Cella et al. and Chada et al.

Applicant points out that claim 26 has been amended to recite a DNA-dependent RNA Pol II promoter to distinguish the instant construct from the construct of Dubensky. Applicant argues that molecule of Dubensky would not function if the RNA-dependent Pol II promoters of Dubensky were substituted for the DNA-dependent RNA Pol II promoters instantly claimed. Applicant states that the motivation to exchange the promoters does not exist because the suggested substitution would render the cassette of Dubensky inoperable.

Applicant's arguments have been fully considered, but are found unpersuasive. As discussed above, Dubensky teaches the promoters instantly claimed for the expression cassette, see claims 1, 2, 7, column 12, lines 54-62, column 55, lines 14-34, column 100, lines 55-56 and column 101, lines 42-57. Therefore, since the promoters of Dubensky and the promoters recited in claim 33 are indistinguishable, the promoters instantly recited would not affect the functionality of the expression cassette of Dubensky.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
July 26, 2003